PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 13

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2475/002629		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06921	20/07/2000	22/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/16		
Applicant KNOLL AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/12/2000	12.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Barnas, C Telephone No. +49 89 2399 7469

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06921

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-40 as originally filed

Claims, No.:

1-52 as originally filed

Drawings, sheets:

1-3 as originally filed

Sequence listing part of the description, pages:

1-6, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 20 (part), 21 (part), 23-35, 38-43, 47, 49-52.

because:

- ☒ the said international application, or the said claims Nos. 20, 21 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
  see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 20 (part), 21 (part), 38, 39, 43 are so unclear that no meaningful opinion could be formed (*specify*):
  see separate sheet

- ☒ the claims, or said claims Nos. 20 (part), 21 (part), 38, 39, 43 are so inadequately supported by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for the said claims Nos. 23-35, 40-42, 47, 49-52.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7, 20, 21, 36, 37, 44-46, 48
	No:	Claims	8-19, 22
Inventive step (IS)	Yes:	Claims	20, 21, 36, 37
	No:	Claims	1-19, 22, 44-46, 48
Industrial applicability (IA)	Yes:	Claims	1-19, 22, 36, 37, 44-46, 48,
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. "A compound capable of altering the expression of NESP55" and "an inhibitor of a polypeptide that is capable of cleaving NESP55" as stated in claims 38, 39 and 43, respectively, are not characterised in structural terms but merely by means of their effects. Thus, this mode of definitions do not relate to a tangible component or group of components, but might comprise an indeterminable number of possible alternatives which may have different chemical compositions. Consequently, the subject matter of said claims is not clearly defined (Art. 6 PCT).

1.2. Furthermore, in the case the above mentioned definitions of compounds, it is necessary that the application discloses the common general knowledge, any technical concept fit for generalization which would enable the skilled person to achieve the envisaged results in its full breadth. Because such a technical concept is lacking in the present application, said claims are regarded as an invitation to perform a research programm which cannot be put into practice without undue burden. Hence, the subject matter of claims 38, 39 and 43 is not sufficiently disclosed (Art. 5 PCT).

Because of the objections under Art. 5 PCT and Art. 6 PCT (see above), claims 38, 39 and 43 have not be subjected to examination.

2. Claims 20 and 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2.1. For the assessment of the present claims 20 and 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: ISCHIA R ET AL: 'MOLECULAR CLONING AND CHARACTERIZATION OF NESP55, A NOVEL CHROMOGRANIN-LIKE PRECURSOR OF A PEPTIDE WITH 5-HT 1B RECEPTOR ANTAGONIST ACTIVITY' JOURNAL OF BIOLOGICAL CHEMISTRY,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD,US, vol. 272, no. 17, 25 April 1997 (1997-04-25), pages 11657-11662, XP000946065 ISSN: 0021-9258

D2: HAYWARD B E ET AL: 'BIDIRECTIONAL IMPRINTING OF A SINGLE GENE: GNAS1 ENCODES MATERNALLY, PATERNALLY, AND BIALLELICALLY DERIVED PROTEINS' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,NATIONAL ACADEMY OF SCIENCE. WASHINGTON,US, vol. 95, December 1998 (1998-12), pages 15475-15480, XP000946062 ISSN: 0027-8424 cited in the application

1. Art. 33(2) PCT, Novelty

The term "fragment" in claim 8 embraces any fragment including fragments consisting of only one amino acid. A "fusion of said ... fragment" as described in said claim, includes, therefore, any known protein. **Claims 8-19 and 22** relate, because of this reason, to known subject matter. Said claims are, therefore, not new.

2. Art. 33(3) PCT, Inventive Step

2.1. D1 (Fig. 2 and p. 11661, right column, "Functional Aspects of NESP55") discloses the peptides LSAL (also named 5-hydroxytryptamine-moduline) and GAIPIRRH which are presumed to be derivable by endoproteolytic cleavage of bovine NESP55. GAIPIRRH is secreted from chromaffin granules while LSAL is an antagonist of the serotonergic 5-HT1B receptor.

D2 (Fig. 1) discloses the sequence of human NESP55 and shows a sequence alignment of bovine and human NESP55 (Fig. 2). By combining D1 and D2 the skilled person would, therefore, know that the human peptides corresponding to the above mentioned bovine peptides are LHAL and GPIPIRRHZ and would further predict that also these human peptides are derived by endoproteolytic cleavage of human NESP55.

Said peptides are, therefore, obvious and **claims 1-8, 14** which embrace said peptides are not inventive. **Claims 9-13, 15, 22, 44 and 46** embracing methods and products connected with said peptides which the skilled person would carry out or produce by applying routine methods are, therefore, also not inventive.

2.2. Also claims 16-18, 45 and 48 are directed to products which the skilled person would carry out or produce by applying routine methods. Because antibodies, polypeptides and polynucleotides produced by routine methods are suitable for use in medicine the feature "for use in medicine", as stated in claims 16-18 and 48, does not render said claims inventive (said feature does also does also not imply the use of the indicated products "as a medicament"). **Claims 16-18, 45 and 48** are, therefore, not inventive.

2.3. The present application does not provide evidence that a pharmaceutical composition as defined in claim 19 can be used for medical treatment (see Re Item VIII, below). Said composition is, therefore, not regarded as relating to any effect. Said claim, therefore, only solves the problem of providing any further composition as such regardless of its likely useful properties. The provision of such a composition, however, does not involve an inventive step. **Claim 19** is, therefore, not inventive.

3. Additional Observations:

D2 closest prior art for claims 20, 21, 36, and 37. The difference to this document is the use of NESP55 for treatment or diagnosis of obesity. The cited prior art does not provide any indication for said use. Claims 20, 21, 36 and 37 seem, therefore, inventive

Re Item VIII
Certain observations on the international application

Arts. 5 and 6 PCT, Lack of Disclosure and Lack of Support, Lack of Clarity

1. The present application does not provide sufficient evidence that any antibody against NESP55 or against an endoproteolytic cleavage product or a variant/fragment/derivative thereof can be successfully used for treating obesity. Claims 20 and 21 are, therefore, not sufficiently disclosed or supported.

2. The application does also not provide evidence if and how the determination of NESP55 expression can be used in order to determine if an individual is likely to become more obese. Claims 36 and 37 are, therefore, also not sufficiently disclosed and not supported.

3. The method of claim 36 does not contain the features which indicate how the NESP55 expression level has to be interpreted in order to determine whether an individual is likely to become or remain obese. Because of the lack of said features, which are considered essential, claim 36 is not clear.